F3 Cont.

of said amplified second target DNA strands as a simultaneous determination of the presence of said first and second target DNA's.

REMARKS

Claims 28, 29, 33 and 36 are pending in the application and have been rejected.

The amendments have been made pursuant to the requirements of Rule 121 of the Rules of Practice. Specifically, the pending claims are written above in clean form and in accordance with 37 C.F.R. § 1.121(c)(1)(i) and § 1.121(c)(3). Pursuant to the requirements of 37 C.F.R.§ 1.121(c)(1)(ii), another version of the amended claims is attached hereto as Exhibit A. This Exhibit A version has been marked up to show all changes made in this amendment relative to the previous version of each claim. As stated hereinabove, the amendments do not constitute new matter. Entry and consideration of the amendments is therefore respectfully requested.

Priority

The Examiner has requested a statement claiming priority to the parent application appear in the first sentence of the specification. Applicants have made the necessary amendment to the specification hereinabove.

Oath/Declaration

The Examiner states that there is no reference to the priority application in the Declaration. Applicants respectfully submit that the Declaration submitted with the application papers for the subject application was that of the priority application. No additional Declaration has been submitted.

Amendments

The Examiner states that a portion of claim 33 has been obliterated by hole punching. Claim 33 as it was prior to the current amendments, appears hereinbelow:

33. A method for the simultaneous amplification and detection of a first target DNA and a second target DNA comprising:

A) simultaneously subjecting the denatured opposing strands of a first target DNA and the denatured opposing strands of a second target DNA to polymerase chain reaction in the presence of:

i) an aqueous composition buffered to a pH of from 7 to 9, and comprising, in the same solution:

first and second primers which are specific to and hybridizable with, respectively, first and second nucleic acid sequences which are in opposing strands of a first target DNA and which are separated from each other along said opposing strands by from 90 to 400 nucleotides, third and fourth primers which are specific to and hybridizable with, respectively, third and fourth nucleic acid sequences which are in opposing strands of a second target DNA which is the same as or different from said first target DNA, said third and fourth nucleic acid sequences being different from said first and second nucleic acid sequences and being separated from each other along said opposing strands of said second target DNA by from 90 to 400 nucleotides, each of said first, second, third and fourth primers having a T_m within the range of from 65 to 74°C, all of said primer T_m's being within about 5°C of each other, said first and second primers having nucleotide lengths which differ from each other by no more than 5 nucleotides, and said

third and fourth primers having nucleotide lengths which differ from each other by no more than 5 nucleotides, and

ii) the additional PCR reagents: a thermostable DNA polymerase, a DNA polymerase cofactor and dNTP's, any or all of said additional PCR reagents being supplied in the same or a different composition as defined in i), to simultaneously amplify said opposing first target DNA strands and said opposing second target DNA strands, provided that in each PCR cycle, each of priming and primer extension are carried out at a temperature within the range of from 62 to 75°C,

B) simultaneously detecting at least one of said amplified first target DNA strands and at least one of said amplified second target DNA strands as a simultaneous determination of the presence of said first and second target DNA's.

Specification

The Examiner avers that the Brief Description of Drawings does not contain separate descriptions of Figures 1-6 and 9 and 10. Applicants have herein reworded the Brief Description of the Drawings hereinabove to provide separate descriptions of each. It is respectfully submitted that this rewording adds no new matter.

The Examiner avers that sequence listing submitted with the application contains hand-written corrections on the first page which were not initialized. The corrections at that location do not go to the merits of the sequence data but rather are corrections to the application number, filing date and classification of the parent application. This application is a divisional application; the Sequence Listing was originally submitted in paper and computer readable form in the parent application. Applicants, in their Response to

Notice to Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures, has made reference to the Sequence listings provided in the parent application. Upon the Examiner's request, a fresh page 1 of the Sequence Listing containing either the original information ("TO BE ASSIGNED") or updated application number, filing date and classification, per the Examiner's preference, will be provided.

Double Patenting

Claims 33, 28, 29 and 36 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 7, 7, 7 & 8 and 2 & 7, respectively, of U.S. Patent No. 6,174,668. The Examiner has stated that a timely-filed terminal disclaimer under 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with the subject application, referring to 37 CFR 1.130(b). Applicants herein state that U.S. Patent No. 6,174,668 is commonly owned with the subject application, and Applicants will file the required terminal disclaimer upon receiving notice of allowable subject matter.

Rejection under 35 USC §112

Claims 33, 28, 29 and 36 were rejected under 35 USC 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Examiner avers that the preamble to claims 33 and 36 states "A method for the simultaneous amplification and detection of a first target DNA and a second target DNA . . .", with the final method step being " . . . simultaneously detecting at least one of said amplified first target DNA strands and at least one of said amplified second target DNA strands as a simultaneous

determination of the presence of said first and second target DNAs".

The Examiner avers it is unclear whether "simultaneous" refers to simultaneous amplification and detection (underscore in original) of the two targets or to amplification of two targets at the same time followed by detection of the two targets at the same time. Applicants have amended claims 33 and 36 herein to specify that the claimed methods are for simultaneous amplification *and subsequent* simultaneous detection of a first target DNA and a second target DNA . . . Applicants respectfully submit that these amendments overcome the rejection and respectfully request this rejection be withdrawn.

Rejection under 35 U.S.C. §102

Claims 33, 28 and 29 were rejected under 35 USC §102(e) as being anticipated by Picone et al. (U.S. Patent No. 5,614,388). In particular, the Examiner avers that Picone et al. teach nucleic acid primers and probes for amplification of select target regions of Legionella genome; that the multiple primer pairs can be used to amplify sequences of the 5S RNA and mip genes of multiple Legionella species (col. 2, lines 18-36); that amplification products are detected using multiple probes immobilized on solid support such as nylon, plastics, glass (col. 4, lines 18-27; col. 8, lines 20-23); that there are two primer pairs for amplification of the mip gene with T_ms of about 65°C and eight primer pairs for amplification of the 5S RNA gene, T_ms of about 68°C; that the length of primers ranges from 18 to 24 base pairs (col. 11, lines 45-55, Table 2); and that the detection probes are 17 to 25 base pairs long and have T_ms from 62

to 69°C, as calculated by the formula T_m = 67.5 + 0.34 (%G+C) - 359/N; that the isolated Legionella genomic DNA is amplified using PCR with primers for mip and 5S RNA genes in the same amplification mix containing PCR buffer of pH 8.9, thermostable Taq polymerase and dNTPs; that the cycling conditions are 95°C for 1 minute, 63°C for 1.5 minutes, 72°C for 7 minutes (col. 16, lines 64-67; col. 17 lines 1-13, 34-36, 64-67; col. 18 lines 1-10); that simultaneous detection of PCR products s achieved either by gel electrophoresis (col. 18 lines 65-67; col. 19, lines 1-13) or by capture on nylon-immobilized capture probes at 50-55°C for 20 minutes (col. 19, lines 14-38; col. 20, lines 1-38).

Applicants have reviewed this rejection and have amended claim 33 in such a way as to incorporate Applicants' formula for calculating primer T_ms therein. When Applicants' formula is applied to the primers of Table 1 of Picone (see table below), the T_ms of the Picone primers range from 61-68°C, that is, at T_ms below those cited by the Examiner as 65°C and 68°C. The T_ms of the Picone probes do not appear relevant to Applicants' pending claims as Applicants do not recite probe Tms therein.

Primer	PT	SEQ ID	Sequence	N	G+C	%G+C	Tm
L mip	69	6	GCA TTG GTG CCG ATT TGG	18	10	55.55	64.44
R mip	70	7	GCT TTG CCA TCA AAT CTT TCT GAA	24	9	37.50	63.79
R mip	181	23	GTT TTG CCA TCA AAT CTT TTT GAA	24	7	29.17	60.96
L5S	82a	10a	GGC GAC TAT AGC GRT TTG GAA	21	10	47.62	64.88
	82b	10b		21	11	52.38	66.50
L5S	159	21	GGC GAC TAT AGC GGT GTG GAA	21	12	57.14	68.12
R5S	80a	9a	GCG ATG ACC TAC TTT CRC ATG A	22	10	45.45	65.00
	80b	9b		22	11	50.00	66.55
R5S	157	22	GCG ATG ACC TAC TTT CGC ATG	21	11	52.38	66.50

R = A or G
Tm = 67.5 + 0.34 x (%G+C) + 395/N

Range tot = 60.96 - 68.12
Range mip only = 60.96 - 64.44
Range 5s only = 64.88-68.12

Applicants' formula for calculating primer T_m values is found in the specification as originally filed at page 12 line 30. Since nothing in Picone et al. teaches or suggests using the formula to calculate the T_ms of the primers, Applicants respectfully submit that claim 33 is patentable over Picone et al., and the rejection respectfully should be withdrawn. Since claims 28 and 29 are dependent of claim 33, Applicants respectfully submit claims 28 and 29 are patentable over Picone et al., as well.

The Examiner states that no references were found teaching or anticipating claim 36, but that is was rejected for other reasons. Applicants respectfully submit that the other reasons are (1) 35 USC 112 matters, which the amendment to claim 36 has, in Applicants' opinion, fully addressed, and (2) the request for a terminal disclaimer which Applicants have offered to submit upon notice of allowable subject matter. Therefore, Applicants respectfully submit that claim 36 is patentable.

It is respectfully submitted that Applicants' claimed methods as amended are patentable over the art cited. Entry of these amendments and allowance of the application on the merits is earnestly solicited.

If a telephone interview would be of assistance in advancing prosecution of the subject application, the Examiner is invited to telephone Applicants' undersigned attorney at the number provided.

If any fees are due in connection with the filing of this amendment, authorization is hereby granted to charge the amount of such fee to Deposit Account No.10-0750/CDS-226/CKG in the name of Johnson & Johnson.

Respectfully submitted,

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Attorney for Applicants
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DATE: November 20, 2002

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EXHIBIT A1

Version Showing Marked-Up Changes to Claims

33. [Amended] A method for the simultaneous amplification and subsequent simultaneous detection of a first target DNA and a second target DNA comprising:

A) simultaneously subjecting the denatured opposing strands of a first target DNA and the denatured opposing strands of a second target DNA to polymerase chain reaction in the presence of:

i) an aqueous composition buffered to a pH of from 7 to 9, and comprising, in the same solution:

first and second primers which are specific to and hybridizable with, respectively, first and second nucleic acid sequences which are in opposing strands of a first target DNA and which are separated from each other along said opposing strands by from 90 to 400 nucleotides, third and fourth primers which are specific to and hybridizable with, respectively, third and fourth nucleic acid sequences which are in opposing strands of a second target DNA which is the same as or different from said first target DNA, said third and fourth nucleic acid sequences being different from said first and second nucleic acid sequences and being separated from each other along said opposing strands of said second target DNA by from 90 to 400 nucleotides, each of said first, second, third and fourth primers having a T_m within the range of from 65 to 74°C, as calculated by the formula $T_m(°C) = 67.5 + 0.34 (\% G + C) - 395/N$, all of said primer T_m's being within about 5°C of each other, said first and second primers having nucleotide lengths which differ from each other by no more than 5

nucleotides, and said third and fourth primers having nucleotide lengths which differ from each other by no more than 5 nucleotides, and

ii) the additional PCR reagents: a thermostable DNA polymerase, a DNA polymerase cofactor and dNTP's, any or all of said additional PCR reagents being supplied in the same or a different composition as defined in i), to simultaneously amplify said opposing first target DNA strands and said opposing second target DNA strands, provided that in each PCR cycle, each of priming and primer extension are carried out at a temperature within the range of from 62 to 75°C,

B) simultaneously detecting at least one of said amplified first target DNA strands and at least one of said amplified second target DNA strands as a simultaneous determination of the presence of said first and second target DNA's.

36. [Amended] A method for the simultaneous amplification and <u>subsequent simultaneous</u> detection of a first target DNA and a second target DNA comprising:

A) simultaneously subjecting the denatured opposing strands of a first target DNA and the denatured opposing strands of a second target DNA to polymerase chain reaction in the presence of:

i) an aqueous composition buffered to a pH of from 7 to 9, and comprising, in the same solution:

first and second primers which are specific to and hybridizable with, respectively, first and second nucleic acid sequences which are in opposing strands of a first target DNA and which are separated from each other along said opposing strands by from 90 to 400 nucleotides,

third and fourth primers which are specific to and hybridizable with, respectively, third and fourth nucleic acid sequences which are in opposing strands of a second target DNA which is the same as or different from said first target DNA, said third and fourth nucleic acid sequences being different from said first and second nucleic acid sequences and being separated from each other along said opposing strands of said second target DNA by from 90 to 400 nucleotides, each of said first, second, third and fourth primers having a T_m within the range of from 67 to 74°C, all of said primer T_m's being within about 2°C of each other, said first and second primers having nucleotide lengths which differ from each other by no more than 5 nucleotides, and said third and fourth primers having nucleotide lengths which differ from each other by no more than 5 nucleotides, and

ii) the additional PCR reagents: a thermostable DNA polymerase, a DNA polymerase cofactor and dNTP's, any or all of said additional PCR reagents being supplied in the same or a different composition as defined in i), to simultaneously amplify said opposing first target DNA strands and said opposing second target DNA strands, provided that in each PCR cycle, priming and primer extension are carried out at the same temperature within the range of from 62 to 75°C,

B) simultaneously detecting at least one of said amplified first target DNA strands and at least one of said amplified second target DNA strands as a simultaneous determination of the presence of said first and second target DNA's.

EXHIBIT A3

Version Showing Marked-up Changes to Specification

IN THE SPECIFICATION:

At page 1, line 3, insert the following:

--**Copending Patent Application Data**

This application is a divisional of parent U.S. Application Serial No. 08/062,023, filed May 14, 1993, now U.S. Patent No. 6,174,668B1.--

At page 8, delete lines 10-21 and replace with the following:

[FIGS. 1-6 are sets of bar graphs showing dye signals for replicate PCR assays of various concentrations of both of hCMV DNA, and HIV-I DNA, as described in Example 2 below.

FIGS. 7 and 8 are sets of bar graphs showing dye signals for replicate PCR assays of various concentrations of HIV-I DNA, as described in Example 3 below.

FIGS. 9 and 10 are sets of bar graphs showing dye signals for replicated PCR assays of various concentrations of hCMV DNA, as described in Example 5 below.]

--FIG. 1 is a bar graph showing dye signals for replicate PCR assays of various concentrations of both hCMV DNA and HIV-DNA, as described in Example 2 below.

FIG. 2 is a bar graph showing dye signals for replicate PCR assays of various concentrations of both hCMV DNA and HIV-DNA, as described in Example 2 below.

FIG. 3 is a bar graph showing dye signals for replicate PCR assays of various concentrations of both hCMV DNA and HIV-DNA, as described in Example 2 below.

FIG. 4 is a bar graph showing dye signals for replicate PCR assays of various concentrations of both hCMV DNA and HIV-DNA, as described in Example 2 below.

FIG. 5 is a bar graph showing dye signals for replicate PCR assays of various concentrations of both hCMV DNA and HIV-DNA, as described in Example 2 below.

FIG. 6 is a bar graph showing dye signals for replicate PCR assays of various concentrations of both hCMV DNA and HIV-DNA, as described in Example 2 below.

FIG. 7 is a bar graph showing dye signals for replicate PCR assays of various concentrations of HIV-I DNA, as described in Example 3 below.

FIG. 8 is a bar graph showing dye signals for replicate PCR assays of various concentrations of HIV-I DNA, as described in Example 3 below.

FIG. 9 is a bar graph showing dye signals for replicated PCR assays of various concentrations of hCMV DNA, as described in Example 5 below.

FIG. 10 is a bar graph showing dye signals for replicated PCR assays of various concentrations of hCMV DNA, as described in Example 5 below. -